A Novel *MGST2* Non-Synonymous Mutation in a Chinese Pedigree with Psoriasis Vulgaris

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A balanced translocation was recently identified in a German psoriasis patient. One of the breakpoints was mapped immediately upstream of the microsomal glutathione *S*-transferase 2 (*MGST2*) gene, suggesting it as a candidate gene. Here, we report the identification of a novel non-synonymous mutation in *MGST2* by a comprehensive sequence analysis of *MGST2*'s coding region in Chinese psoriasis samples. We demonstrate that this mutation co-segregated with the disease phenotype within a Chinese family affected with psoriasis vulgaris and is predicted to have an impact on the normal function of *MGST2* protein. However, the mutation was absent in 551 additional cases and 384 healthy Chinese controls. While requiring independent confirmation, our results suggest that this rare mutation could play a causal role in a small subset of psoriasis individuals.

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INTRODUCTION

Psoriasis (OMIM 177900) is a common cutaneous disorder characterized by inflammation and abnormal epidermal proliferation with a prevalence of 2–3% in Caucasian populations (Nevitt and Hutchinson, 1996) and 0.1–0.3% in Far East populations (Simons, 1949; Yui Yip, 1984). Our previous genome-wide scan provided strong evidence for major psoriasis susceptibility locus PSORS1 and suggestive evidence for PSORS9 in the Chinese population (Zhang *et al.*, 2002). Subsequently, a meta-analysis of six genome-wide linkage data demonstrated that besides PSORS1, PSORS9 is the most convincing linkage locus for psoriasis (Sagoo *et al.*, 2004).

Recently, a German research group identified a balanced translocation in a psoriasis patient and mapped one of its breakpoints into the immediate upstream region of *MGST2* (Tzschach *et al.*, 2006). *MGST2* encodes a protein which catalyzes the conjugation of leukotriene A4 and reduced glutathione to produce leukotriene C4 (Jakobsson *et al.*, 1996). Leukotriene A4 can be further transformed into leukotriene B4, a very potent inductor of hyperproliferation and inflammation. Application of leukotriene B4 to normal human skin can induce changes similar to those found in psoriatic skin (Seyger *et al.*, 1997).

Given these several lines of suggestive evidence for its role in psoriasis pathogenesis, we decided to subject the *MGST2* gene to detailed mutation analysis. This analysis identified a novel but very uncommon non-synonymous mutation predicted to alter the transmembrane structure of *MGST2*, which demonstrated complete co-segregation with the disease phenotype in a small family yielding three informative meioses.

CASE REPORT

The index case was a 29-year-old male who developed psoriasis at 26 years of age and presented with plaque psoriasis over the extremities and lower trunk. His affected brother, a 28-year-old male who developed psoriasis at 24 years of age, also presented with plaque psoriasis on both hands, but no other areas of psoriatic skin were found. There was evidence neither for the involvement of the soles of the feet nor for psoriatic arthritis. Histological examination confirmed the diagnosis of psoriasis in both patients.

The patients did not have any other current illnesses, any allergies or significant past medical history. The index case's parents and another brother did not have psoriasis. However, one of his paternal uncles was diagnosed with plaque psoriasis, suggesting that the index case's father might be a non-symptomatic patient. Unfortunately, this affected uncle

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Abbreviation: MGST2, microsomal glutathione S-transferase 2

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accidentally died at 37 years of age without any children, and his DNA sample was thus not available for analysis.

RESULTS AND DISCUSSION

We first performed mutation analysis of the whole coding region of *MGST2* by sequencing 48 familial cases of psoriasis and 48 matched healthy controls. In addition to five known exons coding for the common transcript of *MGST2*, there are 11 additional putative coding exons within the *MGST2* region (http://www.ncbi.nlm.nih.gov/AceView/). We sequenced all the 16 known and suggested exons, exon–intron boundaries and approximately 2,000 bp of 5′ flanking region. Ten variants were identified, and five were new single nucleotide polymorphisms. Of the five newly identified single nucleotide polymorphisms, four were non-coding, located within either the 5′ flanking region (g.-1227C→T) or intronic regions (g.80T→C, g.9878T→C and g.5492GT→C). Only one non-synonymous mutation Q76K (g.29245C→A) within the exon 3 was identified in the index case.

Further analysis of the Q76K mutation in all four family members of the index case indicated that his affected brother and non-sympotamatic father were both heterozygous for this mutation (Figure 1), but his unaffected brother and mother did not carry the mutation. This suggests that the mutation co-segregated with the disease phenotype within the pedigree of the index case yielding three informative meioses. We further investigated the mutation in 384 healthy controls, but the mutation was absent. Furthermore, our TMpred – Prediction analysis suggested that *MGST2* protein contains two hydrophobic transmembrane domains (Figure 2) and the Q76K mutation is located within one of the predicted transmembrane domains. The mutation could interfere with proper protein folding and/or packing by replacing a polar glutamine with a positively charged lysine within the transmembrane domain. Therefore, our results suggested that this mutation could be a causal variant for psoriasis. We further analyzed this mutation in an additional 187 familial and 364 sporadic cases of psoriasis. This mutation was not detected in any of the 551 cases, suggesting that this mutation is very rare in both familial and sporadic cases and might only play a causal role in a small subset of psoriasis individuals.

In summary, our comprehensive sequence analysis of the entire coding region of *MGST2* identified a novel non-synonymous mutation in the third exon of the *MGST2* transcript, which demonstrated complete co-segregation with psoriasis in a small family and is predicted to have an impact on the normal function of *MGST2* protein. However, the heterozygous father was non-penetrant for the mutation, and this mutation was not observed in any other families, nor in a set of Chinese cases and controls. Thus, while this mutation deserves further investigation in additional psoriasis families, it is unlikely to account for much of the genetic burden of psoriasis. Further searching is therefore warranted for the yet-to-be-identified psoriasis disease gene within PSORS9.

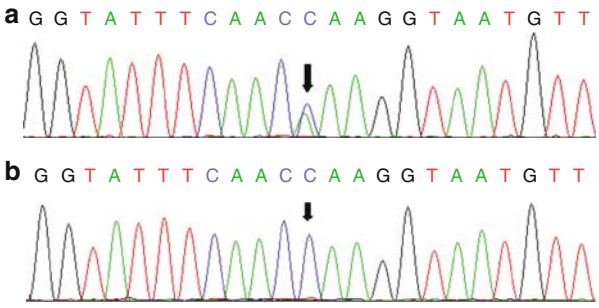

Figure 1. Electropherograms from sequence analysis of the (a) index case and (b) his unaffected mother.

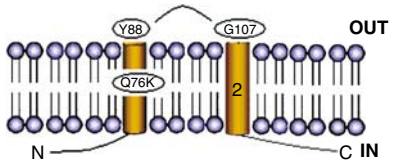

Figure 2. The predicted topological model of *MGST2* with two predicted transmembrane domains illustrated. The Q75K mutation is located within one of the predicted transmembrane domains.

MATERIALS AND METHODS

In addition to the index case and his first-degree relatives, we recruited an additional 187 familial patients, 364 sporadic patients, and 384 healthy controls from the Dermatology Department of the Anhui Medical University. All the samples are Chinese and were recruited with informed content. The study was approved by the medical ethics committee of the Anhui Medical University and was conducted according to the Declaration of Helsinki Principles.

Genomic DNA was extracted from peripheral blood leukocytes using standard procedures (Miller *et al.*, 1988). Primers for sequence analysis were listed in Supplementary Table S1. Sequence analysis was performed as previously described (Zhang *et al.*, 2004).

Transmembrane domains and their orientations within the *MGST2* protein were predicted using the TMpred program (http://www.ch.embnet.org/software/TMPRED_form.html). The algorithm is based on the statistical analysis of TMbase, a database of naturally occurring transmembrane proteins. The prediction is made using a combination of several weight-matrices for scoring (Hoffmann and Stoffel, 1993).

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Table S1. PCR primer sequences used in sequencing analysis.

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